In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

K.O., parent of A.F., a minor, Petitioner,	*	No. 13-472V
	*	Special Master Christian J. Moran
	*	Filed: July 7, 2016
v.	*	Reissued: January 3, 2017
SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	Entitlement; Pneumococcal Conjugate ("PCV") Vaccine; Opsoclonus Myoclonus Syndrome ("OMS").

Ronald C. Homer and Meredith Daniels, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for petitioner;
Heather L. Pearlman, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

K.O. filed a petition on behalf of her minor son, A.F., alleging that the pneumococcal conjugate ("PCV") vaccine caused him to develop opsoclonus myoclonus syndrome ("OMS"). K.O. is seeking compensation pursuant to the National Childhood Vaccine Injury Compensation Program, codified at 42 U.S.C. § 300aa−10 through 34 (2012).

To connect the PCV vaccine and A.F.'s OMS, K.O. relied upon the opinion of a pediatric neurologist, Spencer Weig. Dr. Weig opined that A.F. developed OMS on August 25, 2010, asserting that the PCV vaccination A.F. received on July 14, 2010, provoked the condition under the theory of molecular mimicry.

The Secretary disagreed with K.O.'s claim. The Secretary presented the opinion of neurologist Eric Lancaster. Dr. Lancaster opined that the onset of

[1] After this decision was issued, the petitioner filed a motion to redact her name to initials pursuant to Vaccine Rule 18(b). That motion was granted. Order, filed Nov. 30, 2016.

A.F.'s OMS was August 28, 2010, and asserted that the medical evidence did not support the theory proposed by Dr. Weig.

K.O.'s case falters for two independent reasons. First, the theory she presents, molecular mimicry, is far too general to be persuasive. She has not offered sufficient evidentiary justification for a finding that Dr. Weig's opinion is reliable. Second, the onset of A.F.'s OMS occurred outside the time that both Dr. Weig and Dr. Lancaster accepted as medically acceptable. Because K.O. did not prove, by a preponderance of the evidence, that the PCV vaccine can cause OMS, and did not show A.F.'s OMS arose in the acceptable time, K.O. did not meet her burden of proof. Thus, she is not entitled to compensation.

I. Background[2]

Section A provides a brief overview of OMS. Section B summarizes the experts' qualifications. Section C delineates the relevant events in A.F.'s medical history.

[2] The undersigned has considered all the evidence. Cf. Moriarty v. Sec'y of Health & Human Servs., No. 2015-5072, 2016 WL 1358616 (Fed. Cir. Apr. 6, 2016) (stating special master erred in not considering the entire record). Although the undersigned does not discuss all the evidence, the undersigned discusses the evidence (documentary and testimonial) that the undersigned finds most relevant. The process of determining the relevancy of any piece of evidence is informed by the undersigned's experience as a special master generally. The undersigned has reviewed the expert reports several times, beginning when they were initially filed. In preparing the order requesting briefs before the hearing, the undersigned reviewed the expert reports and the articles cited in those reports. The parties provided their views of the relevance of the articles in their pre-hearing briefs. The parties' briefs, in turn, provided a foundation for asking questions at the hearing. The witnesses' testimony further refined and highlighted the most important articles that the parties discussed in their briefs after the hearing. The undersigned is reasonably confident that this process has brought to his attention any piece of evidence that would significantly contribute to analyzing K.O.'s claim. See Vaccine Rule 8(b)(1).

A. Opsoclonus Myoclonus Syndrome

OMS is a rare neurological condition defined by acute onset of rapid and chaotic eye movements (opsoclonus) and jerking of the limbs and trunks (myoclonus) in conjunction with other conditions, including ataxia and behavioral irritability. Exhibit 18, tab C (Katherine K. Matthay, Opsoclonus myoclonus syndrome in neuroblastoma: a report from a workshop on the dancing eyes syndrome at the advances in neuroblastoma meeting in Genoa, Italy, 2004, 228 Cancer Lett. 275 (2005)) at 276; exhibit D (Barbara Hero, Update on Pediatric Opsoclonus Myoclonus Syndrome, 44 Neuropediatrics 324 (2013)) at 324; exhibit 18, tab D (K. Ki Pang, A prospective study of the presentation and management of dancing eye syndrome/opsoclonus–myoclonus syndrome in the United Kingdom, 14 European J. of Pediatr. Neurol., 156 (2010)) at 156. Most, but not all, pediatric patients with OMS also have a diagnosis of a neuroblastoma.[3] The etiology of OMS is believed to be autoimmune in nature. Exhibit 18, tab B (M. Kinsbourne, Myoclonic encephalopathy of infants, 25 J. Neurol. Neurosurg. Psychiatr. 271 (1962)) at 276; exhibit 18, tab C at 276-77; exhibit D at 324; Tr. 52-53, 61, 154.

OMS is diagnosed upon the presentation of a patient with various prodromal[4] symptoms with irritability being the most common. Neurologic symptoms of ataxia, falling, and myoclonus are most often experienced with behavioral problems becoming more prevalent. OMS is commonly misdiagnosed as acute cerebellitis. Exhibit J (Elizabeth D. Tate, Neuroepidemiologic Trends in 105 US Cases of Pediatric Opsoclonus-Myoclonus Syndrome, 22 J. of Pediatr. Oncol. Nurs., 8 (2005)) at 10.

B. Expert Qualifications

K.O. relies upon the expert opinion of Spencer Weig. Dr. Weig is a board-certified pediatrician and neurologist with a special qualification in child neurology. Exhibit 18 at 1; exhibit 19 at 2. He graduated from Mt. Sinai School of

[3] A neuroblastoma is a sarcoma consisting of malignant neuroblasts, usually arising in the autonomic nervous system or in the adrenal medulla. It is considered a type of neuroepithelial tumor and affects mostly infants and children up to 10 years of age. Dorland's Illus. Med. Dictionary at 1263 (32d ed. 2012).

[4] A prodrome is a premonitory symptom or precursor; a symptom indicating the onset of a disease. Dorland's at 1522.

Medicine in 1973 and, after practicing for several years, completed residencies and a fellowship in child neurology. He practiced child and adult neurology continuously for 24 years. Exhibit 18 at 1. Dr. Weig has treated 10 to 12 patients with opsoclonus myoclonus syndrome over the course of his career. Exhibit 18 at 1; Tr. 10. He remains active in the Departments of Neurology and Pediatrics at the University of North Carolina at Chapel Hill School of Medicine. Exhibit 18 at 1.

The Secretary relies upon the expert opinion of Eric Lancaster. Dr. Lancaster completed his PhD focused on neuroscience and MD degrees at the University of Maryland in 2002 and 2003, respectively. He completed a residency in neurology and multiple fellowships in neuromuscular study. He is the author of 22 peer-reviewed publications with many concerning autoimmune neurological disorders. Exhibit A at 1; exhibit B at 3-4. Dr. Lancaster's current practice primarily focuses on research of autoimmune brain and nerve diseases. Tr. 101. Dr. Lancaster has treated one patient with opsoclonus myoclonus syndrome. Exhibit A at 1. He currently serves as an assistant professor of neurology at the University of Pennsylvania. Exhibit B at 1.

C. A.F.'s Medical History

A.F. was born on July 15, 2009, and developed normally for the first year. See generally exhibit 5 at 1-24. At his one-year child health check on July 14, 2010, A.F. received the PCV vaccine. Id. at 23.

A few weeks later, on August 11, 2010, A.F. was seen by pediatrician Meredith Saillant presenting with a carbuncle[5] that she eventually diagnosed as "furuncle of face."[6] Id. at 25. In Dr. Lancaster's opinion, the presence of the furuncle within a month before onset of OMS was a better temporal fit for an "autoimmune encephalitis after immune stimuli" as the mechanism of A.F.'s OMS than the PCV vaccination. Tr. 147. Dr. Weig disagreed, stating that between the furuncle and vaccine, the vaccine more likely than not triggered the OMS. Tr. 156.

[5] A carbuncle is a necrotizing infection of skin and subcutaneous tissue composed of a cluster of boils (furuncles), usually due to Staphylococcus aureus, with multiple formed or incipient drainage sinuses. Dorland's, at 289; Tr. 146, 169.

[6] A furuncle is a painful nodule formed in the skin by circumscribed inflammation of the dermis and subcutaneous tissue after staphylococci enter through the hair follicles. Dorland's, at 751; Tr. 146, 169.

K.O. recalled A.F. experiencing constipation on August 25, 2010. She gave him prune juice and noted some improvement. Exhibit 13 at ¶ 4. A.F. had an eye exam on August 27, 2010, with unremarkable results and Dr. Rebecca Maida concluding that "[A.F.'s] eyes are healthy." Exhibit 8 at 7. The normal eye exam, Dr. Weig opined, indicated that A.F. was not experiencing opsoclonus at the time. Tr. 37. Dr. Lancaster asserted that a normal eye exam rules out opsoclonus and he further asserted that a doctor would not miss opsoclonus during an eye exam. Tr. 151.

The day after his eye examination, A.F. was taken to the emergency room due to increased fussiness, crying, drooling, unsteadiness, and lack of bowel movement. Exhibit 4 at 8. An abdominal x-ray revealed a "large amount of stool." A.F. was discharged in good condition with instructions for the family to use glycerin suppositories and prune juice. Id. at 9-10.

The following day, on August 29, 2010, A.F. was taken to the emergency room again for being "inconsolable of late" and complaints that he "[c]ried inconsolably for 4 [hours]" when being put down for a nap. Exhibit 6 at 282, 287; Tr. 19. The family reported that A.F. was more uncoordinated than usual, wobbling and flopping, and that he had been constipated for several days. Exhibit 6 at 287. The family also reported that A.F. was no longer constipated or fussy as he had been the previous night. Id. at 282. The doctor's neurologic exam was normal, noting that A.F. was "[f]ussy with exam but consolable." Id. at 283. A consultation with a neurologist was arranged. Id. at 284-86.

Dr. Weig opined that the irritability and inconsolable crying were prodromal symptoms of OMS. Dr. Weig also asserted that A.F.'s irritability and inconsolable crying started no later than August 25, 2010, based on the affidavit of K.O. and the medical records of Dr. David Coulter. Tr. 39-41. Dr. Lancaster disagreed, asserting that the medical records and histories provided by K.O. indicate that A.F. was constipated on August 25, 2010, and did not experience any OMS-like symptoms until later on August 28. Tr. 107-08.

During a consultation on August 29, 2010, neurologist David Coulter documented the concerns of lethargy, inconsolability, and coordination issues. Exhibit 6 at 290. Dr. Coulter noted some weakness attributing it to "the setting of constipation or mild illness (though he has had no evidence of recent illness)." Id. at 289. Dr. Coulter concluded that the neurologic exam was normal with follow up suggested in two weeks. Id.

A.F. saw a physician with Dr. Saillant's practice, Marshall Reiner, on August 30, 2010, for a follow-up after the emergency room visit. While the parents complained that A.F. had regressed and been "unsteady" for the past two days, Dr. Reiner's impression was that "the child's actions are normal for age." The diagnosis was ataxia with a referral to a neurologist. Exhibit 5 at 25. Dr. Saillant saw A.F. on August 31, 2010, with continued complaints of irritability, constipation, and unsteadiness that had not improved. Exhibit 5 at 26. Dr. Saillant noted that A.F. was "markedly different from the last time I saw him a few weeks ago" and that his balance was "severly [sic] compromised." Id. She confirmed the diagnosis of ataxia and expressed her concerns for closer neurological evaluation and an MRI with Dr. Coulter, scheduling an appointment for the following day. Id. at 26-27.

Upon review of the past medical history and examination on September 1, 2010, Dr. Coulter diagnosed A.F. with acute cerebellar ataxia. Exhibit 6 at 279-80. Dr. Coulter's notes state that the family had reported to him that A.F. had been fine on August 27, 2010, with an onset of symptoms on August 28 and worsening on August 29. Id. at 280-82. Five days later, on September 6, 2010, A.F. was taken back to the emergency room due to concerns that he was "losing motor skills." Id. at 262. He was admitted for further evaluation. Id. at 264.

On September 7, 2010, during the hospital stay, Kara Smith noted that A.F. had lost the ability to "sit independently, pull to stand and to cruise, all of which he had previously." Dr. Smith diagnosed A.F. with opsoclonus myoclonus syndrome stating "[A.F.'s] history and exam is quite concerning and he offers opsoclonus as well as myoclonus." Dr. Smith coordinated further imaging studies with A.F.'s neuroimmunologist, Mark Gorman, to rule out a neural crest tumor, such as a neuroblastoma. Exhibit 6 at 269-70, exhibit 17 at 4. A.F. was discharged the following day.

Under the supervision of Dr. Gorman, A.F. was readmitted on September 14, 2010, for MRI and MIBG[7] scanning. Exhibit 6 at 259. There was no evidence of a neuroblastoma. Id., Tr. 95-96, 160. The notes from Dr. Gorman summarized A.F.'s medical history including his receipt of the PCV vaccine. Dr. Gorman

[7] An MIBG scintiscan is a type of imaging test. It uses a radioactive substance (called a tracer) and a scanner to find or confirm the presence of pheochromocytoma and neuroblastoma. These are types of tumors that affect nerve tissue. "MIBG scintiscan," A.D.A.M. Medical Encyclopedia, (June 21, 2016, 10:45 AM), https://www.nlm.nih.gov/medlineplus/ency/article/003830.htm.

stated developmental changes began "[o]n 8/28." Exhibit 6 at 247. Dr. Gorman confirmed the OMS diagnosis, stating "[t]he presentation is [entirely] consistent with OMS and meets 2004 Genoa criteria for the diagnosis." Id. at 249; see generally exhibit 18, tab C. Dr. Gorman recommended immunosuppressive therapy. Exhibit 6 at 250.

A.F. returned to Dr. Gorman for a follow up visit on November 5, 2010, when Dr. Gorman noted that A.F. had "idiopathic OMS" being treated with immunosuppressive therapy that was going well. Exhibit 6 at 201-02. Dr. Lancaster opined that Dr. Gorman's impression that the OMS was "idiopathic" is an indication that a cause or triggering event was sought, but one was not found. Tr. 142-43.

Several months after Dr. Gorman's follow up appointment, pediatric neuro-ophthalmologist Gena Heidary evaluated A.F. on June 2, 2011. Dr. Heidary's impression of A.F.'s OMS was that while the etiology was unclear, "there is a question of a reaction to the pneumococcal vaccine number 13 as this was the only thing that antedated the onset of his symptoms." Exhibit 6 at 143. A.F. returned to Dr. Heidary on September 15, 2011, and she noted that the OMS had resolved and he was "doing extremely well." Id. at 119.

II. Procedural History

On July 12, 2013, K.O. filed a petition on behalf of her minor son, A.F., alleging that the PCV vaccine caused him to develop OMS. K.O. filed medical records, exhibits 1-12, on October 28 and 30, 2013. Affidavits were filed on December 17, 2013 and outstanding medical records filed on December 20, 2013. Exhibits 13-15.

On January 7, 2014, the Secretary filed her report pursuant to Vaccine Rule 4. The Secretary maintained that K.O. had failed to demonstrate causation. Resp't's Rep. at 13. The Secretary argued that K.O. did not offer reliable scientific evidence that demonstrated a causal relationship between the PCV vaccination and OMS. Although the Secretary noted that pediatric neuro-ophthalmologist Gena Heidary stated that she "thought" the PCV vaccination was secondary to A.F.'s OMS, the Secretary asserted that Dr. Heidary's opinion was contradicted by all of A.F.'s treating physicians who did not mention such an association, but merely noted the temporal relationship. Id. at 13.

During a January 13, 2014 status conference to discuss the Rule 4 report, K.O. stated that she would retain an expert to opine on her case after the parties

discussed the possibility of settlement. K.O. filed additional medical records and a response to the Rule 4 report on January 29, 2014. K.O. answered questions presented regarding medical records asserting that all requests made by respondent were satisfied. Pet'r's Resp., filed Jan. 29, 2014.

On February 4, 2014, K.O. filed a status report proposing a May 5, 2014 deadline for her expert report. The undersigned issued draft Instructions to Witnesses Offering Opinion Testimony (hereinafter "proposed instructions") on February 12, 2014. The undersigned explained that expert reports are filed in advance of the hearing and provide all parties and the special master notice of the contents of the testimony. Therefore, the proposed instructions ordered that any expert's report would, most likely, constitute the expert's testimony on direct examination. The undersigned further explained that the purpose of this requirement was two-fold: 1) to ensure a complete report that presented the expert's opinions and bases for those opinions, and 2) to decrease time spent in hearings repeating the content of the expert report.

The undersigned ordered K.O. to file any comments to the proposed instructions by February 28, 2014, and her expert report by May 5, 2014. On March 7, 2014, K.O. filed her Opposition to the Court's Proposed Instructions to Witnesses Offering Opinion Testimony. Presenting several objections to the proposed instructions, K.O. relied primarily upon Vaccine Rule 8. K.O. asserted that Rule 8(b)(2) allows petitioners to present evidence in the manner in which they choose and that there is no authority given to special masters to require evidence be presented in a specific format. Pet'r's Opp. at 4. K.O. further asserted that expert reports are evidence as governed by Vaccine Rule 8(b) and therefore cannot be limited to the written report. Id. at 5.

Additionally, K.O. argued that expert testimony in complex cases warranted oral presentation and cited two previous cases where the undersigned has stated that "oral testimony may be more persuasive than written records." Id. at 6-7. K.O. asserted that the proposed instructions were in conflict with Federal Rules of Civil Procedure ("FRCP") 26(a)(2)(B) and the role of a special master as outlined in Vaccine Rule 3(b)(2) because they would lead to a "more rigid, less flexible, and more adversarial process" contrary to Congress's intent. Id. at 9-10. K.O. also made a general objection to the fairness of the proposed instructions as they applied to petitioners. Id. at 10-11.

The undersigned issued an order for expert reports and addressed K.O.'s objections on April 17, 2014. This order mandated that the expert reports comply with the proposed instructions previously set forth and that the reports would

constitute direct testimony. The undersigned drew from other instances where written direct testimony had been used in non-jury cases by similar courts with the most instructive instance being the Tax Court. The undersigned analogized the Court of Federal Claims and the Office of Special Masters to the Tax Court in three ways. First, both are Article I tribunals. Second, both are devoted to one subject matter. Third, both hear cases without a jury. The undersigned noted that the Tax Court Rules of Practice and Procedure, specifically Rule 143(g), provided that testimony need not be presented orally. Additionally, FRCP 43(a) removed the oral testimony requirement. The undersigned reasoned that this was instructive because Court of Federal Claims Rule 43 is identical to FRCP 43. The undersigned cited cases in which the Court of Federal Claims and the Tax Court had received direct testimony from experts in the form of written reports.

The undersigned further observed that there is no statutory restriction prevents the Office of Special Masters from using expert reports as direct testimony. In addressing K.O.'s fairness objections, the undersigned determined that they were unpersuasive as the order applied to both parties and was designed to facilitate flexibility in the presentation of evidence allowing experts weeks to draft comprehensive reports with assistance of counsel for development.

K.O. filed her expert report, supporting literature, and the curriculum vitae from Dr. Weig on July 11, 2014. Exhibits 18-19. On July 16, 2014, K.O. filed a Renewed Opposition to the Court's Orders dated February 12, 2014 and April 17, 2014 and Motion to Vacate the Orders. K.O. renewed her objections that special masters lacked authority to require expert reports as direct testimony, precluding oral testimony was a detriment to petitioners being able to present the opinion of the expert fully, and that the special master had gone beyond his duties in mandating the instructions. See generally Pet'r's Renewed Opp., filed July 16, 2014. K.O. also introduced specific objections to the instructions. Id. at 10-12.

During the ensuing status conference to discuss Dr. Weig's report, the undersigned determined that most of petitioner's outstanding motions were moot due to Dr. Weig answering the questions posited by the instructions in his report. Order, issued July 25, 2014. The Secretary filed an expert report with supporting literature, following the same instructions as K.O., as well as a curriculum vitae, from Dr. Lancaster on October 1, 2014. Exhibits A-Q. In the ensuing status conference to discuss Dr. Lancaster's report, the undersigned ordered Dr. Lancaster to provide the basis for his assertion that "PCV contains no antigens expressed in a normal brain." Reminding K.O. that Dr. Weig's reports may constitute his direct testimony, the undersigned ordered a supplemental report to respond to Dr. Lancaster. At that time, the parties discussed exploring settlement.

The Secretary filed Dr. Lancaster's supplemental expert report with supporting literature on November 5, 2014. Exhibits R-T. On December 12, 2014, K.O. filed Dr. Weig's responsive expert report with supporting literature. Exhibit 20. On January 13, 2015, the Secretary filed a status report indicating that, despite settlement efforts, she desired to defend the case. During a January 23, 2015 status conference, the undersigned questioned whether a fact hearing would be needed to settle the question of onset.

The Secretary filed a supplemental expert report from Dr. Lancaster on February 9, 2015. Exhibit U. The parties proposed mutually convenient dates for an expert hearing on entitlement and a one-day hearing was set for August 13, 2015. Pet'r's Status Rep., filed Mar. 2, 2015. The undersigned issued a pre-hearing order setting the dates for pre-hearing submissions and the pre-hearing status conference. Order, issued Apr. 23, 2015; see also order, issued Apr. 6, 2015. K.O. filed her pre-hearing brief on June 24, 2015. In an order issued June 29, 2015, the undersigned reiterated that the reports of the experts, upon careful review, would constitute direct testimony due to any oral direct testimony likely being duplicative. The undersigned allowed K.O. to submit a supplemental statement identifying the portions of Dr. Weig's opinion that she believed should be presented orally due to her requests for oral presentation. The Secretary was also afforded the opportunity to submit a responsive supplemental statement from Dr. Lancaster.

On July 9, 2015, K.O. filed a supplemental statement asserting that oral direct testimony from Dr. Weig was required to present the dispute regarding onset of OMS symptoms, complex theories, a logical sequence of cause and effect showing that the vaccination was the reason for the injury, and showing a proximate temporal relationship between the vaccination and injury. On July 13, 2015, the Secretary filed her pre-hearing brief.

An expert hearing was held on August 10, 2015, in Washington, DC. Both Dr. Weig and Dr. Lancaster testified at the hearing. Both testified in accord with their reports.

Dr. Weig testified that the onset of symptoms was late August 2010, opining the date to be August 25, 2010, based on K.O.'s affidavit and the August 29, 2010 medical records from Dr. David Coulter. Tr. 74-75. He stated that K.O. noticed the irritability in late August which is consistent with the timing of OMS symptom onset. Tr. 18-19, exhibit 13 (K.O.'s affidavit) at 1-2. The medical records from the hospital then provided a documented parental statement of the symptoms presenting since three days prior to that August 28 visit. Tr. 19-20, exhibit 18 (Dr.

Weig's report) at 7. Dr. Weig stated that the irritability noticed by the parents and crying at night, supported an onset date of August 25 because these behaviors were the early symptoms of the disease. Tr. 19-20, 23; exhibit 18 at 4.

Dr. Weig explained that A.F.'s normal eye exam results on August 27 were unremarkable because, in his professional experience, a patient could be asymptomatic for opsoclonus and later exhibit symptoms. Tr. 38-39, 94. Dr. Weig ruled out constipation as the cause of A.F.'s irritability due to the duration and prolonged period of crying. The duration of the irritability instead pointed to a typical prodromal symptom of OMS. Tr. 39-41, exhibit 18 at 7.

Dr. Weig opined that it was more likely than not that A.F.'s OMS was vaccine-induced because extensive testing ruled out possible alternate causes, such as neuroblastoma, or alternate theories. Tr. 95, 169; exhibit 18 at 9.

K.O. had approximately 30 minutes of direct examination with Dr. Weig. K.O. was also able to ask Dr. Weig any additional questions or gain clarification on re-direct examination after the Secretary cross-examined and the undersigned examined Dr. Weig.

The Secretary presented the testimony of Eric Lancaster at the hearing. Dr. Lancaster testified that, based on the totality of the medical records, the irritability A.F. experienced on August 25, 2010, was due to constipation with which he was diagnosed and for which he was treated. Tr. 108, exhibit A at 12. He opined that the onset of OMS was three days later, on August 28, as confirmed by the contemporaneous medical records. Tr. 107, exhibit A at 13.

Dr. Lancaster acknowledged Dr. Heidary's records possibly linking the vaccination to OMS as K.O. suggested, but asserted that her notes indicated obscurity regarding causation and an inability to understand her thought process fully. Tr. 141-42. In contrast to Dr. Weig's opinion, Dr. Lancaster stated that A.F.'s normal eye exam was "very helpful for ruling out opsoclonus" as it would be "very unlikely, for any eye doctor to miss that." The normal exam and physician indication that A.F. was negative of any symptoms weighed against onset prior to August 28. Tr. 150-51, exhibit A at 3, 12; exhibit U at 2.

Dr. Lancaster opined that the furuncle present prior to the onset of A.F.'s neurological symptoms provided a better temporal fit as a potential triggering infection. Tr. 146-47, exhibit A at 13. He further explained that while the cause of A.F.'s OMS was more likely idiopathic, the furuncle was a more plausible trigger than the vaccination. Tr. 155-56, exhibit A at 13.

Overall, the process of expert reports as direct testimony worked well. Both Dr. Weig and Dr. Lancaster presented their opinions (in writing and orally) thoughtfully. When the undersigned asked Dr. Weig his opinion regarding the instructions issued to him for preparing his expert reports, Dr. Weig testified that the instructions "helped me organize my – my thoughts, my analysis of the records. I didn't think it was artificial either. I mean, I found it helpful." Tr. 171.

On August 21, 2015, the undersigned issued an order for post-hearing briefs. While the case was still pending, K.O. filed a motion for attorneys' fees and costs on an interim basis with the Secretary filing a response shortly thereafter. K.O. filed her post-hearing brief on October 22, 2015. The Secretary submitted her post-hearing brief on November 18, 2015, with K.O. filing a reply on December 3, 2015. K.O. filed an additional motion for interim fees and costs on June 20, 2016. The case is now ripe for a decision.

III. Standards for Adjudication

A petitioner is required to establish her case by a preponderance of the evidence. 42 U.S.C. § 300aa–13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health &Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

The elements of K.O.'s case are set forth in the often cited passage from the Federal Circuit's decision in Althen: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

IV. Analysis

As mentioned in the introduction of this decision, K.O.'s case fails to be persuasive with respect to two of the Althen prongs. First, K.O. has not presented evidence of sufficient quantity or quality that supports a finding that molecular mimicry is a reliable mechanism persuasively explaining how the PCV vaccine can cause OMS. This shortcoming is addressed in section A below.

The second problem with K.O.'s case is that the timing does not fit. Both Dr. Weig and Dr. Lancaster opined that an acceptable interval between vaccination and the onset of OMS would encompass 42 days. Neither expert offered opinions that an onset of more than 42 days would be medically acceptable. As explained in section B below, the records created in August and September 2010, are much more consistent with a finding that A.F. started to experience OMS 45 days after vaccination.

K.O.'s failure to establish either a persuasive medical theory (Althen prong 1) or an acceptable temporal relationship (Althen prong three) resolves her case. Because either finding is dispositive, the analysis of the remaining Althen prong (a logical sequence of cause an effect) is relatively short. See section C. Finally, section D considers a potential cause for A.F.'s OMS that is unrelated to the PCV vaccine.

A. Theory

K.O.'s burden is to present "a medical theory causally connecting the vaccination and the injury." Althen, 418 F.3d 1274, 1278.

1. K.O. must prove causation by a preponderance of the evidence.

To establish the first prong of Althen, K.O. must provide "a reliable medical or scientific explanation." La Londe v. Sec'y of Health & Human Servs., 110 Fed. Cl. 184, 201 (2013), aff'd sub nom. LaLonde v. Sec'y of Health & Human Servs., 746 F.3d 1334, 1339-40 (Fed. Cir. 2014). A special master may require additional evidence supporting a theory of molecular mimicry to find that the theory is related to the petitioner. W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1360 (Fed. Cir. 2013); Hunt v. Sec'y of Health & Human Servs., 123 Fed. Cl. 509, 524-25 (2015) (special master properly followed W.C. and was not arbitrary in finding molecular mimicry not persuasive); Crutchfield v. Sec'y of Health & Human Servs., 125 Fed. Cl. 251, 263 (2014) (special master was not arbitrary in finding that the petitioner's expert failed to demonstrate any similarities between the vaccine and a relevant part of the body).

2. Evidence relating to theory

Collectively, the parties' evidence relating to the proposition that PCV vaccines can cause OMS via molecular mimicry falls into five broad categories: (a) literature about vaccines and OMS, (b) an article by Pranzatelli, (c) studies on homology, (d) an admission by Dr. Lancaster, and (e) an admission by the Secretary in other cases.[8] These topics are explored below.

a. Literature

In support of their respective positions, the parties submitted medical articles discussing vaccines and disorders of the central nervous system, including OMS. The medical articles fall into two groups: an epidemiologic study and four case reports.

Because these articles are part of the record, they must be considered. 42 U.S.C. § 300aa−13(a); Moriarty, 2016 WL 1358616 at *9-10. An assessment of these articles is consistent with Terran's endorsement of the flexible Daubert test, which authorizes special masters to consider, among other factors, whether an

[8] Some of this evidence originated with the Secretary because the Secretary "is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief." Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008).

expert's opinion appears in peer review literature and whether the opinion has been tested. Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999), citing Daubert v. Merrell Dow Pharmaceuticals, 509 U.S. 579, 593-94 (1993).

In weighing the relative value of the articles, the undersigned follows the guidance of the Federal Judicial Center. The Federal Judicial Center has published a series of guides designed "to assist judges ... in reaching an informed and reasoned assessment concerning the basis of expert evidence." Jerome P. Kassirer and Gladys Kessler, Reference Manual on Scientific Evidence, Preface, (3d ed. 2011). The guidance from the Federal Judicial Center translates to the Vaccine Program because the burden of proof in an off-Table case, like K.O.'s case, is "the traditional tort standard." Moberly, 592 F.3d at 1322.

1) Epidemiology

According to the Federal Judicial Center, "[e]pidemiologic studies have been well received by courts deciding cases involving toxic substances." Michael D. Green et al., Reference Manual on Scientific Evidence, Reference Guide on Epidemiology, 549 n.2 (3d ed. 2011) (citing cases). "Epidemiologic evidence identifies agents that are associated with an increased risk of disease in groups of individuals, quantifies the amount of excess disease that is associated with an agent, and provides a profile of the type of individual who is likely to contract a disease after being exposed to an agent." Id. at 552. The authors of this guide from the Federal Judicial Center emphasize that "an association is not equivalent to causation." Id. "In evaluating epidemiologic evidence, the key questions, then, are the extent to which a study's limitations compromise its findings and permit inferences about causation." Id. at 553.

Consistent with the instruction from the Federal Judicial Center, the Federal Circuit has long endorsed special masters' consideration of epidemiologic evidence. W.C., 704 F.3d at 1361; Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1149 (Fed. Cir. 1992) ("epidemiological studies are probative evidence relevant to causation"). However, special masters may not go so far as to require petitioners in off-Table cases to present epidemiologic evidence to establish that a

particular vaccine can cause a particular injury. Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006).[9]

Here, the record contains one epidemiologic study. Exhibit K (Hung Fu Tseng et al., Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal vaccine in children, 31 Vaccine 2578 (2013)). The researchers relied upon information held in the Vaccine Safety Datalink.[10] The authors compared the number of adverse events following approximately 600,000 doses of the PCV-13 vaccine with the number of adverse events following administration of PCV-7. After reviewing medical records, the researchers found that PCV-13 was not associated with an increased risk of encephalopathy. Id. at 2580.

In their reports, first Dr. Lancaster and then Dr. Weig commented on the Tseng study.[11] Based on Tseng, Dr. Lancaster concluded that the "medical literature therefore does not support any association between PCV13 and OMS." Exhibit A at 10. Dr. Weig challenged Dr. Lancaster's reliance on the Tseng study. Dr. Weig's starting points were that the incidence of OMS is approximately one case per five million children and that the non-neuroblastoma incidence is approximately one case per ten million children. From here, Dr. Weig argued: "In a sample size of 500,000, we would only expect to see .1 child (1/10 of a child) with OMS. Given the incredibly low incidence rate of OMS, the sample size of [the] Tseng study is underpowered to detect even one incidence of OMS." Exhibit 20 at 2.

---

[9] If a petitioner presented reliable epidemiologic evidence that a vaccine is associated with a statistically significant increased risk of developing a disease, the Secretary would likely agree to resolve the case. See National Injury Compensation Program: Revisions to the Vaccine Injury Table, 80 Fed. Reg. 45132-01 (proposed July 29, 2015) (to be codified at 42 C.F.R. § 100.3) (discussing epidemiological studies supporting modifications to the list of injuries presumptively caused by vaccines).

[10] For more information regarding the Vaccine Safety Datalink, see Parsley v. Sec'y of Health & Human Servs., No. 08-781V, 2011 WL 2463539, at *10 n.33 (Fed. Cl. Spec. Mstr. May 27, 2011); Werderitsh v. Sec'y of Health & Human Servs., No. 99-319V, 2005 WL 3320041 (Fed. Cl. Spec. Mstr. Nov. 10, 2005) (denying motion for production of documents).

[11] Dr. Weig has no training or experience in epidemiology. Tr. 12. Dr. Lancaster has taken one course on epidemiology and biostatistics while obtaining his medical degree. Tr. 103.

At hearing, Dr. Lancaster changed his position. He stated "Dr. Weig has a good point, that the disease is very rare, which makes it very hard to fully power to detect it." Tr. 133-34. Nevertheless, without citing any authority, the Secretary argued that the Tseng study remains "evidence to be considered." Resp't's Posth'g Br. at 11 n.3. In contrast, K.O. contended that the only value of the Tseng study is to call into question Dr. Lancaster's credibility. Pet'r's Resp. at 8-9.

It is important to remember that K.O. has the burden to show that the PCV vaccine can cause OMS. Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). In finding no increased risk of OMS after PCV-13, the Tseng study does not help K.O. meet her burden. Whether the Tseng study would be a reliable basis for an opinion that PCV vaccinations cannot cause OMS is another question and a question that is not germane to this case's outcome. The Secretary does not bear the burden of establishing that it is impossible for PCV vaccinations to cause OMS.

2) Case Reports

Unlike Tseng, which the Secretary's expert introduced, K.O. relied upon a set of four case reports. See Pet'r's Preh'g Br. at 14, 20; Pet'r's Posth'g Br. at 25-28; Pet'r's Resp. at 9-10. In her view, "case reports . . . supplement and bolster her other evidence of causation." Pet'r's Resp. at 10.

Again, the undersigned follows the lead of the Federal Judicial Center. A pertinent guide states "[a]necdotal evidence usually amounts to reports that events of one kind are followed by events of another kind. Typically, the reports are not even sufficient to show association, because there is no comparison group." David H. Kaye and David A. Freedman, Reference Manual on Scientific Evidence, Reference Guide on Statistics, at 218. These authors also state "some courts have suggested that attempts to infer causation from anecdotal reports are inadmissible as unsound methodology under Daubert." Id. at 217 n. 14 (citing cases).

The only Federal Circuit case to discuss the value of case reports in the Vaccine Program found no error in a special master's giving the case reports little weight. In a series of five cases involving auto-immune hepatitis, the undersigned special master rejected case reports as evidence of causation. Porter v. Sec'y of Health & Human Servs., No. 99–639, 2008 WL 4483740, at *13 (Fed. Cl. Spec. Mstr. Oct. 2, 2008). Under the caption of a different case, a judge at the Court of Federal Claims disagreed with this weighing of evidence. Rotoli v. Sec'y of Health & Human Servs., 89 Fed. Cl. 71, 86-87 (2009).

When the Federal Circuit reviewed the special master's decision, the Federal Circuit stated that "[t]he special master found that the remaining two articles, both describing single case studies, did not contain any meaningful analysis about causation." Porter v. Sec'y of Health & Human Servs., 663 F.3d 1242, 1253 (Fed. Cir. 2012). The Federal Circuit also stated that the "decision reveals a thorough and careful evaluation of all the evidence including ... medical literature." Id. at 1254. Admittedly, the discourse on case reports in Porter is indirect and there may come a time when the Federal Circuit addresses the evidentiary value of case reports in the Vaccine Program more directly. Until that future Federal Circuit case, the undersigned relies upon Porter, which endorsed a view that single case studies did not contain any meaningful analysis of causation.

It is interesting to juxtapose case reports with epidemiologic studies. Case reports are generally seen as holding less evidentiary value than epidemiologic studies. Campbell v. Sec'y of Health & Human Servs., 97 Fed. Cl. 660, 668 (2011).[12] Here, what is more useful — an observational study involving more than a half million people or a handful of anecdotes? As discussed above, K.O. and Dr. Weig present an insightful criticism of the Tseng study: it was not sufficiently powered to detect increases in OMS. Yet, with regard to the case reports, K.O. and Dr. Weig have not presented any persuasive argument why the case reports rise even to the level of circumstantial indicia of causation. Tr. 44-45; exhibit 18. As the Court of Appeals for the Eleventh Circuit stated, case reports "do not offer the underlying toxicological data in a scientifically reliable form to satisfy Daubert." McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1253-54 (11th Cir. 2005).

The foregoing assessment describes the limited value of case reports generally. Here, the case reports K.O. and Dr. Weig identify have even less value because they report a sequence in which a vaccine, but not a vaccine against pneumococcus, precede the onset of OMS. Exhibit 18, tab B (Kinsbourne); Exhibit 18, tab L (Nicholas Christoff, Myoclonic encephalopathy of infants: A report of two cases and observations on related disorders, 21 Arch Neurol. 229 (1969)); Exhibit 18, tab N (James McCarthy & James Filiano, Opsoclonus myoclonus after human papilloma virus vaccine in a pediatric patient, 15 Parkinsonism and Related Disorders 792 (2009)); Exhibit 18, tab M (F. Lapenna et

[12] Although Campbell recognized that case reports have less value, Campbell continued: "Nevertheless, the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight. See, e.g., Rotoli, 89 Fed. Cl. 86-87." After Campbell was issued, the Federal Circuit reversed Rotoli. Porter, 663 F.3d at 1245.

al., Post-vaccinic opsoclonus- myoclonus syndrome: a case report, 6 Parkinsonism and Related Disorders 241 (2000)).

An expert may "extrapolate from existing data," Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 743 (2009), and use "circumstantial evidence," Althen, 418 F.3d at 1280. But, the reasons for the extrapolation should be transparent and persuasive. Here, Dr. Weig did not offer any persuasive reasons for extrapolating from the rubella vaccine, HPV vaccine, DTP vaccine, and polio vaccine, to the PCV vaccine.

After considering the case reports, the testimony about the case reports, and the briefs containing arguments about the case reports, the undersigned chooses to give the four case reports negligible weight. See Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099, 1108 (Fed. Cir. 1996) ("Congress desired the special masters to have very wide discretion with respect to the evidence they would consider and the weight to be assigned that evidence"). They are not a reliable basis for finding causation. Consequently, the evidence relating to the reliability of the theory of molecular mimicry will be explored in detail. The following three sections (the Pranzatelli article, homology, and Dr. Lancaster's admission) concern molecular mimicry.

b. Pranzatelli article

Dr. Michael Pranzatelli is considered one of the leading researchers for OMS. Tr. 24. When Dr. Weig was asked to identify the articles that most strongly supported his opinion regarding molecular mimicry, Dr. Weig cited a review article that Dr. Pranzatelli wrote in 1996. Tr. 53, citing exhibit 18, tab G (Michael R. Pranzatelli, The immunopharmacology of the opsoclonus-myoclonus syndrome, 19 Clin. Neuropharmacology 1 (1996)).

In that lengthy article, Dr. Pranzatelli proposes molecular mimicry as one among several possible etiologic theories. Exhibit 18, tab G at 21-22. In this context, Dr. Pranzatelli states that "Cross-reactivity between neural crest-derived tumors and brain antigens…in paraneoplastic cases is also very plausible, given their shared embryology." Id. at 22.[13] Dr. Pranzatelli returns to molecular mimicry in his conclusion. "A peripheral induction mechanism involving

[13] K.O. frequently cited these pages of the Pranzatelli article. Pet'r's Preh'g Br., filed July 9, 2015, at 12, 19; Pet'r's Posth'g Br. at 19; Pet'r's Posth'g Resp. at 8; see also Tr. 25.

molecular mimicry or one of several other possible mechanisms leads to immune system dysregulation, which transiently allows otherwise for hidden autoaggression against cross-reactive brain antigens. Although immunizations are logical candidates for costimulation in peripheral induction in children, if there is an adult counterpart, it is unknown." Id. at 36. Dr. Weig interpreted this passage as indicating that Dr. Pranzatelli was "certainly… open to the idea of immunization as a potential initiating factor in children." Tr. 26.

Dr. Weig's assessment that Dr. Pranzatelli was "open" to the idea that immunizations may contribute to the onset of OMS appears accurate. Dr. Pranzatelli also discussed vaccinations in another part of his long article. Dr. Pranzatelli's list of environmental factors that are "likely to be very important in OMS" includes viruses, bacteria, and immunizations. Yet, Dr. Pranzatelli recognized that "Assessment of the potential effects of immunization on the onset of OMS is not simple." Id. at 18-19. Dr. Weig understood Dr. Pranzatelli as wanting to avoid the logical pitfall known as "post hoc ergo propter hoc." In other words, it is wrong to conclude that because a second event occurs after a first event, the first event caused the second event. Tr. 60. In his article, Dr. Pranzatelli recommended an epidemiologic study. Exhibit 18, tab G at 19.

At hearing, K.O. referenced Dr. Pranzatelli's statement that a reaction to a tumor and virus producing OMS "presented both a puzzle and a clue." Dr. Weig explained that the puzzle is determining what a virus or bacterium have in common with a form of cancer. The clue would be that the body responds to fight a tumor in the same manner it responds to fight a virus or bacterium. Tr. 57-58.

Dr. Pranzatelli made this statement as part of his thesis for his research into the mechanism of action of current therapy. Exhibit 18, tab G at 2. Dr. Pranzatelli ultimately stated that the virus was not directly encephalogenic in OMS cases associated with viral infection. Id. at 4. Specifically on vaccinations, he states that molecular mimicry is a "possible mechanism." Id. at 21, 36.

In the Secretary's post-hearing brief, she challenged K.O.'s reliance on the Pranzatelli article in several respects. First, the Secretary observes that Dr. Pranzatelli did not state "that vaccines in general (let alone the PCV vaccine specifically) can cause OMS" via molecular mimicry. Second, Dr. Weig's conclusion that Dr. Pranzatelli was "open" to vaccines as a causative factor "is insufficient for petitioner to meet her burden." Third, the Secretary argues that the lack of validation of molecular mimicry outside the context of a neuroblastoma in the 20 years since Dr. Pranzatelli wrote the article is "telling." Resp't's Posth'g

Br., filed Nov. 18, 2015, at 12. K.O.'s reply brief did not answer these specific criticisms of the Pranzatelli article.

Whether developments in the last two decades have supported the proposal that vaccines can cause OMS via molecular mimicry is considered next.

c. Homology

A premise for molecular mimicry is that a particular antigen (say, a vaccine) shares that molecular structure with some part of the human body such that the immune system's attack on the antigen is misdirected to the host's own tissue. Exhibit 18, tab G (Pranzatelli) at 21. The medical term for similarity in structure is homology. Dorland's at 868.

The degree of homology between two proteins can be determined using a method known as blast sequencing according to an article Dr. Weig submitted. Exhibit 18, tab H (Paul M. Candler et al., Post-streptococcal opsoclonus-myoclonus syndrome associated with anti-neuroleukin antibodies, J. Neurol. Neurosurgery Psychiatry 507 (2006)) at 509; see also Wirt v. Sec'y of Health & Human Servs., No. 11-118V, 2014 WL 1911421, *8 (Fed. Cl. Spec. Mstr. April 18, 2014). The article cites to a website maintained by the National Institutes of Health.

The Secretary's expert, Dr. Lancaster, explained the experiment the Candler group conducted. Dr. Lancaster also criticized the experiment in certain respects, but these perceived flaws are not particularly important to the outcome of K.O.'s case. Tr. 118-22. More significantly, K.O.'s expert, Dr. Weig, struggled to explain the Candler experiment. Tr. 53-55. When asked to explain what a blast sequence is and whether it could be used on the pneumococcal vaccine, Dr. Weig said that he did not have the background to answer those questions. Tr. 55-56.

On cross-examination, Dr. Weig was asked whether he was aware of any homology between the PCV vaccine and brain cells. Dr. Weig stated that he did not know. Dr. Weig was also asked whether he knew of any homology between the pneumococcal bacteria (the target of the PCV vaccine) and brain cells, Dr. Weig again stated that he did not know. Tr. 85. Dr. Weig's lack of knowledge creates a considerable gap in K.O.'s case.

Special masters may consider whether the expert's opinion can be and has been tested. Terran, 195 F.3d at 1316, citing Daubert, 509 U.S. at 593-94. Here, Dr. Weig is assuming that there is homology between the PCV vaccine and brain

tissue. However, Dr. Weig lacks a background to determine the accuracy of his assumption. This lack of testing constitutes a reason for finding Dr. Weig unpersuasive. See Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 135 (2011) ("Without any empirical evidence that the theory [of molecular mimicry] actually applies to the influenza vaccine and [transverse myelitis], the first prong of Althen would be rendered meaningless"), aff'd without opinion, 463 F. App'x 932 (Fed. Cir. 2012).

d. Admission by Dr. Lancaster

K.O. argued that a showing of homology between the PCV vaccine and brain tissue is not needed because Dr. Lancaster has accepted molecular mimicry as a theory to explain how neuroblastomas can lead to OMS. Pet'r's Posth'g Br., filed Oct. 22, 2015, at 20; Pet'r's Posth'g Resp., filed Dec. 3, 2015, at 7. To review, a neuroblastoma is a tumor of embryonic cells that develop into a nerve cell or neuron. See Dorland's at 1263 (defining neuroblast and neuroblastoma), 1668 (defining sarcoma). Neuroblastomas are found in approximately 50 percent of OMS cases.

The frequency of cases in which neuroblastomas precede OMS has led to a conclusion that neuroblastomas cause OMS. How neuroblastomas cause OMS has not been elucidated. Tr. 42-44, 112. Dr. Pranzatelli's 1996 article proposes that: "While the initial immune response is appropriately directed to eradicating virus or tumor, the immune response becomes secondarily pathological." Exhibit 18, tab G at 21. Dr. Pranzatelli, as discussed above, suggested molecular mimicry as one theory to explain the harmful response of the immune system.

Dr. Lancaster stated, "in the case of patients with neuroblastoma, [I think] that molecular mimicry is – is close to the correct concept." Tr. 116. Later, Dr. Lancaster clarified that molecular mimicry in cases with a neuroblastoma is "not yet firmly established because we don't have the specific antigen." Tr. 135.

While Dr. Lancaster accepted molecular mimicry as a "highly likely" link between neuroblastomas and OMS, Dr. Lancaster distinguished viruses as a potential source of cross-reactivity. "Given how very different viruses are from human beings, it would be unusual for some component of the virus to very closely resemble some component of the brain." Tr. 117. Dr. Lancaster's opinion was that viruses might cause OMS through some process other than molecular mimicry. Tr. 117-18, 135.

K.O. charges Dr. Lancaster with being inconsistent in two respects. First, K.O. argues that Dr. Pranzatelli proposed molecular mimicry as a theory by which neuroblastomas (tumors) and infections could lead to OMS. Pet'r's Posth'g Br. at 20; Pet'r's Posth'g Resp. at 7. In this respect, K.O. is only partially correct. It is true that Dr. Pranzatelli suggested molecular mimicry for tumors as well as infections. Exhibit 18, tab G at 21. However, molecular mimicry is not the only theory that Dr. Pranzatelli proposed. Id. at 16 ("Response to Viruses"), 19-22. Thus, Dr. Pranzatelli's article can accommodate molecular mimicry for neuroblastomas and some other theory for infectious agents.

Second, K.O. argues that Dr. Lancaster is being inconsistent because science has not found the pathway for either neuroblastomas or infections. Under K.O.'s logic, because the lack of knowledge about the target antigen does not prevent Dr. Lancaster from accepting molecular mimicry as a method to explain the connection between neuroblastomas and OMS, this same lack of knowledge should not prevent Dr. Lancaster from accepting molecular mimicry as a method to connect infections and OMS. Pet'r's Preh'g Br. at 22; Pet'r's Posth'g Resp. at 7.

Here, too, K.O.'s argument misses its mark. Because neuroblastomas are essentially malignant nerve cells, it is easy to see how the immune system's response to neuroblastomas could be misdirected against other nerve cells, such as those found in the brain. See Tr. 51 (Dr. Weig). That step is relatively short. In contrast, the PCV vaccine does not contain nerve cells. Thus, an attempt to join the PCV vaccine and brain cells affected in OMS requires a much longer jump.[14]

In short, K.O. is not persuasive in arguing that because molecular mimicry may be valid in some situations not involving vaccines, molecular mimicry also should be accepted as a reliable theory in a situation involving vaccines.

[14] K.O. could have shortened the gap between the PCV vaccine and brain cells by presenting evidence that they are homologous. However, as discussed above, K.O. did not narrow the gap.

e. Admission by the Secretary

Finally, K.O. argues that her theory is reliable because the Secretary has agreed to settle other cases involving OMS. Pet'r's Resp. at 3-4. Procedurally, the argument was raised too late. K.O. could have offered this same argument in either her pre-hearing brief or her initial post-hearing brief. But, she did not. Non-jurisdictional arguments that are raised for the first time in a reply brief are typically considered waived. See Demodulation, Inc. v. United States, 103 Fed. Cl. 794, 808 (2012). As attorneys experienced in the Vaccine Program, K.O.'s counsel should have known that raising an argument this late is improper.

More significantly, settlements are not considered admissions that can be used to establish a fact based upon a settlement. See Woods v. Sec'y of Health & Human Servs., 105 Fed. Cl. 148, (2012) (settlement of cases cannot equate to the finding of reasonable basis); R.V. and E.V. v. Sec'y of Health & Human Servs., No. 08-504V, 2015 WL 1396357 (Fed. Cl. Spec. Mstr. March 6, 2015) (rejecting argument that the Secretary was judicially estopped from litigating an argument based upon a settlement of another case), mot. for rev. denied, 127 Fed. Cl. 136 (2016). Thus, the resolution of other cases involving OMS does not meaningfully change the analysis of the evidence K.O. and the Secretary presented in this case.

f. Synopsis

Through Dr. Weig, K.O. has presented a theory to explain how the PCV vaccine can cause OMS. However, K.O. has not presented a reliable basis for finding this theory persuasive. Consequently, K.O. has not established her burden of proof regarding Althen prong one.

B. Timing

K.O. must establish a "proximate temporal relationship" between the PCV vaccination and the onset of A.F.'s opsoclonus myoclonus. Bazan, 539 F.3d at 1352. This formulation implies that the third prong from Althen actually contains two parts. First, there must be a showing that a range of time is "acceptable" to infer causation. Second, there must be a showing that the vaccinee's disease arose in this acceptable time. Shapiro v. Sec'y of Health & Human Servs., 101 Fed. Cl. 532, 542-43 (2011), recons. denied after remand on other grounds, 105 Fed. Cl. 353 (2012), aff'd per curiam, 503 F. App'x 952 (Fed. Cir. 2013).

1. Medically Acceptable Interval

The first part of the third prong of Althen requires K.O. to show a time which is "medically acceptable" for an injury to appear after a vaccination, assuming that the vaccination caused the injury. Bazan 539 F.3d at 1352.

Here, the parties generally agree that an interval from which inferring causation is acceptable is from one to six weeks. Dr. Weig provided this estimate in his report, exhibit 18 at 7, and based his estimate on a 1994 report from the Institute of Medicine ("IOM") that considered whether vaccines against tetanus, diphtheria, and pertussis could cause demyelinating diseases. When asked during the hearing if he could explain the 42 day limit, Dr. Weig stated: "I don't know. It's just there." Tr. 65.

Dr. Lancaster also relied upon the 1994 IOM report but stated that the IOM report states that onset is more likely to occur within seven to 21 days of vaccination. Tr. 137-38; exhibit A at 12. Thus, Dr. Lancaster explained that while the IOM provides 42 days within the range for onset, it is the upper limit of plausibility. Tr. 140.

Based upon entire record, the undersigned finds that an acceptable interval extends to 42 days. The record does not contain any persuasive basis for extending this period past 42 days. As Dr. Lancaster explained, the IOM found that vaccines might produce a demyelinating disease within seven to 21 days. The IOM, then, further extended the 21 days to 42 days to account for any outliers. Tr. 140; exhibit Q (Institute of Medicine, Adverse Events of Vaccines Evidence and Causality (Kathleen Stratton et al. eds. (2011))) at 535; exhibit P (Institute of Medicine, Adverse Events of Vaccines Evidence and Causality (Kathleen Stratton et al. eds. (1994))) at 26.

Therefore, to establish the third prong of Althen, K.O. must establish that A.F.'s OMS developed within 42 days of his PCV 13 vaccination.[15]

[15] Although a finding of 42 days (and not 43) may appear arbitrary, the persuasive evidence does not go further than 42 days. "At the margins of any judgment call, reasonable minds may differ as to the judgment reached. Such is the natural consequence of regulatory line-drawing, much as the natural consequence of judicial line-drawing will permit of marginal dispute. But that is not to say that the line-drawing exercise lacks reason or is arbitrary." Haggar Apparel Co. v. United States, 222 F.3d 1337, 1342 (Fed. Cir. 2000).

2. Onset of OMS

Unlike the agreeing opinions that an acceptable interval was up to 42 days, the parties have considerable dispute about when A.F. first began to manifest problems of his OMS. As previously discussed, the onset of OMS is sometimes marked by the presentation of prodromal symptoms such as irritability, behavioral disturbances, and ataxia. K.O. asserts that the prodromal symptoms were present on August 25, 2010 (42 days after vaccination). The Secretary disagrees and proposes August 28, 2010, as the onset date (45 days after vaccination).[16]

Dr. Weig first opined an onset date as far back as August 20, 2010. Exhibit 18 at 7. When asked how he determined this date, he answered "Well, not directly in the medical record. That was working backwards from…K.O.'s report of late August and then knowing, in my mind, that the symptoms began on the -- you know, the first mention we have in there is August 25th, that I thought it was probably started a few days earlier." Tr. 73. Dr. Weig agreed that the medical records did not support this onset date. Id. K.O. recalled that in "late August 2010" A.F. experienced difficulty sleeping and sensitivity to light. Exhibit 13 ¶ 3. She stated on August 25, 2010, A.F. was constipated but this improved with after giving him prune juice. Id. at ¶4.

In the absence of a reliable foundation for his opinion that A.F. started to experience OMS on August 20, 2010, Dr. Weig came up with another date. He proposed August 25, 2010. Tr. 19-20. The medical records show A.F. was irritable and constipated. Exhibit 4 at 8-9, 12-13, 15; see also Tr. 18. Dr. Weig agreed that A.F. was constipated, but contended that the degree of irritability described made it prodromal. Tr. 39-40. K.O. did not address the constipation otherwise.

In K.O.'s post-hearing brief, she asserts that determining the onset of OMS in children of A.F.'s age is difficult. For this argument, she relies on her expert, Dr. Weig, who stated that behavioral issues, which can be prodromal symptoms of OMS, are more difficult to assess in a child one-year to two-years old. Pet'r's Posth'g Br. at 16; Tr. 17. Dr. Weig states that while "exact timing of onset of symptomatology is frequently quite difficult to ascertain with absolute precision," the sleep disturbances and irritability that A.F. experienced made it "evident that

[16] This difference of three days is significant because it changes the onset from 42 to 45 days, which then falls outside of the accepted range as established by the IOM report.

by 8/25/2010" these were symptoms consistent with the onset of OMS. Exhibit 18 at 7.

The Secretary's expert, Dr. Lancaster, stated that A.F. was experiencing constipation based on the totality of the medical records on August 25, 2010. He stated that K.O. reported several times in the record that the symptoms of irritability subsided once A.F. passed a hard stool. Tr. 107-08. The resolution of A.F.'s irritability after he moved his bowels suggested that constipation was causing the irritability. If a brain-based neurologic disorder had been causing A.F.'s irritability, then the irritability would have continued after the bowel movement. Thus, August 25, 2010 is not the date of onset of A.F.'s OMS.

Here, the persuasive evidence indicates that the onset of A.F.'s OMS was on August 28, 2010. Dr. Lancaster provided an onset date of August 28 based on the medical records. Exhibit A at 13; Tr. 150. Several medical records point to an onset of August 28, 2010. These include: exhibit 6 at 282-86 (Dr. Shrivastava's notes on August 29, 2010, stating "Mom noted his coordination seemed to be off a little yesterday."); exhibit 6 at 286-89 (Dr. Coulter's notes on August 29, 2010, stating "[A.F.]…presents today with a one day [history] of 'wobbliness and floppiness'… Of note: five days prior to presentation, when he was 'constipated' with mom noting that he had increased straining, and needed prunes to pass a hard stool."); exhibit 6 at 290-91 (Dr. Viccari's notes on August 29, 2010, stating "The patient is a 13-month-old male crying inconsolably on and off since yesterday. History of being constipated."); exhibit 5 at 25 (Dr. Reiner's notes on August 30, 2010, stating "Unsteady, different sense of balance, past 2 days."); exhibit 5 at 26-7 (Dr. Saillant's notes on August 31, 2010, stating "3 days ago was irritable and had some constipation and thought to have imbalance/dizziness."); exhibit 6 at 279-80 (Dr. Coulter's notes on September 1, 2010, stating "When I saw [A.F.] on September 1st, his parents again noted that [A.F.] had been pretty normal on Friday, August 27th, and in fact had seen the eye doctor that day and had a normal examination."); exhibit 8 at 4 (phone call from A.F.'s father to Bennet Family Eye care stating "since after appt [A.F.'s] leg's wobbly, trouble sitting more clumsy").

This abundant evidence, which K.O. did not address in her reply brief, supports a finding that the onset of OMS was August 28, 2010. This finding means that 45 days elapsed after the vaccination. Because K.O. offered no basis for extending the accepted interval past 42 days (see Pet'r's Posth'g Br. at 37), the timing for A.F. does not work. See Bazan, 539 F.3d 1352 (a petitioner fails to satisfy the third prong of Althen when too much time elapses between vaccination and onset).

C. Logical Sequence of Cause and Effect

The remaining prong from Althen is "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Althen, 418 F.3d at 1278. Evidence particularly relevant to this inquiry is the view of any treating doctor. Capizzano, 440 F.3d at 1326.

Here, the parties rely upon different views expressed by two doctors. K.O. cites pediatric neuro-ophthalmologist Gena Heidary's June 2, 2011 report. Pet'r's Posth'g Br. at 32-33. Dr. Heidary wrote: while the etiology was unclear, "there is a question of a reaction to the pneumococcal vaccine number 13 as this was the only thing that antedated the onset of his symptoms." Exhibit 6 at 143.

The Secretary, in contrast, mentions the November 5, 2010 report of pediatric neuro-immunologist Mark Gorman. Dr. Gorman's early history showed that he was aware of A.F.'s receipt of the PCV vaccine. Exhibit 6 at 247. Yet, on November 5, 2010, Dr. Gorman described A.F.'s OMS as "idiopathic," meaning Dr. Gorman did not know the cause of the OMS. Exhibit 6 at 201-02.

Dr. Heidary's report does not assist K.O. in any significant way. Dr. Heidary received a history that A.F. had received that PCV vaccination three weeks prior to symptom development. Exhibit 6 at 143. But, this history is erroneous. The actual interval between vaccination and onset was longer than Dr. Heidary understood. When a treating doctor receives an inaccurate history, the special master is not required to defer to that doctor's opinion regarding causation. Dobrydnev v. Sec'y of Health & Human Servs., 566 F. App'x 976, 992-83, reh'g denied, (Fed. Cir. 2014), cert. denied, 135 S. Ct. 1560, 191 L. Ed. 2d 639 (2015).

Moreover, Dr. Heidary's actual words are "there is a question of a reaction." This wording does not indicate that Dr. Heidary believes, on a more-likely-than-not basis, that the vaccination caused A.F.'s OMS. See Paterek v. Sec'y of Health & Human Servs., 527 F. App'x 875 (Fed. Cir. 2013) (indicating that a treating doctor's statement that vaccine-causation was "not impossible" does not establish causation).

In addition to the problems with Dr. Heidary's report, other evidence suggests that there is not a logical sequence between A.F.'s vaccination and his OMS. As discussed above, K.O. has not presented a reliable basis for crediting the theory that PCV vaccine can cause OMS. As a matter of logic, if there is no showing that the vaccine can cause an injury, there cannot be a basis for finding the vaccine did cause the injury. Similarly, K.O. has not established an acceptable

temporal relationship. Again, as a matter of logic, if the injury occurs outside of the time expected, then a finding of causation would not be logical.

D. Alternate Causes

Finally, some precedent suggests that special masters, in considering whether petitioners have met their burden regarding prong two, should consider whether petitioners have ruled out any other potential causes for the injury. See Doe 11 v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1358 (Fed. Cir. 2010); Contreras v. Sec'y of Health & Human Servs., 107 Fed. Cl. 280, 296 (2012), mot. for rev. granted after remand, 116 Fed. Cl. 472 (2014), mot. for rev. denied after third remand, 121 Fed. Cl. 230 (2015), appeal docketed, No. 15-5097 (Fed. Cir. June 15, 2015).

Here, Dr. Lancaster proposed that A.F.'s OMS was "idiopathic." Exhibit A at 13; Tr. 156. Alternatively, between the two factors that were considered as possible causes (the furuncle and the vaccination), Dr. Lancaster ranked the furuncle as more likely than the vaccination. In Dr. Lancaster's opinion, the furuncle was a stronger candidate than the vaccination (but still less likely than an unknown cause) because A.F. experienced the furuncle in closer temporal proximity than the vaccination. Tr. 147.

K.O.'s brief addresses only the Secretary's contention that the most likely cause of A.F.'s OMS was an unknown cause. K.O. makes a creditable argument that assuming she has met her burden of proof regarding the three Althen prongs, the Secretary cannot rely upon an idiopathic cause to defeat the claim for compensation. Pet'r's Posth'g Br. at 42-43, citing Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 547-48 (Fed. Cir. 1994). However, the predicate of this argument — that K.O. established the three Althen prongs with preponderant evidence — is not correct for the reasons explained above. Therefore, the burden of proof did not shift to the Secretary. LaLonde, 746 F.3d at 1340.

To the extent that the presence of potential alternative causes bears on the petitioner's burden regarding Althen prong two, K.O. errs when she states "respondent has offered no evidence of an alternative cause leading to the onset of A.F.'s OMS." Pet'r's Reply at 19 (emphasis in original). As just mentioned, Dr. Lancaster proposed that the furuncle was a more likely cause than the vaccination. Thus, it is not correct to say the Secretary has "no evidence." Similarly, K.O. argues "Respondent's 'ranking' of the potential causes from most likely to least likely as 1) idiopathic, 2) skin infection and 3) PCV vaccine is baseless." Pet'r's

Reply at 20. The Secretary's argument is not "baseless" because it is based on Dr. Lancaster's opinion.

For the furuncle, K.O. essentially places all her eggs in one basket — an argument that because Dr. Lancaster could not say that the furuncle was the likely cause of the injury, his opinion is "wholly irrelevant." Pet'r's Reply at 20. However, K.O. has not cited any precedent that the Secretary must establish an alternative cause as more likely than not before a petitioner must address the proposed alternative cause.[17] The case law seems to be heading in the opposite direction. See Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373, 1380 (Fed. Cir. 2012) (causation cannot be evaluated without addressing the "elephant in the room" of evidence indicating a separate cause for the injury). Once the argument about relevancy is passed, K.O. says nothing about the furuncle. She cannot challenge the fact that A.F. had a furuncle on August 11, 2010, which is 17 days before August 28, 2010.

K.O.'s expert, Dr. Weig, offers little assistance to her. (K.O. did not cite any testimony about the furuncle from him in her post-hearing briefs.) At hearing, when asked why the bacteria that is the source of the furuncle was not a trigger for molecular mimicry leading to A.F.'s OMS, Dr. Weig stated that "it's more likely than not that the vaccine would be the cause." He went on to state that he discounted the bacteria because he knew of no known associations between skin infections and opsoclonus myoclonus syndrome. Tr. 169-70. This argument essentially undercuts K.O.'s assertion that the PCV vaccine caused A.F.'s OMS as she presented no evidence of known associations between the PCV vaccine and OMS.

Thus, the analysis has come full circle. The first problem with K.O.'s case is that she has not demonstrated, at a preponderance of the evidence level, that the PCV vaccine can cause OMS. As discussed at length above, the cause of OMS is not known in approximately 50 percent of the cases. In these non-neuroblastoma cases, there is a lack of supporting evidence for any proposed causes, including viruses, bacteria, and vaccines. The fact that bacteria have not been established as a cause of OMS is analytically distinct from whether the PCV vaccine can cause OMS. See Caves, 100 Fed. Cl. at 140-41. The second problem with K.O.'s case is

[17] Knudsen's comments arose in a case in which the petitioners had established their child suffered an on-Table injury, meaning the petitioners were presumptively entitled to compensation. Here, K.O. has not met her burden of proof.

that the timing between A.F.'s vaccination and the onset of OMS is not a match. The timing problem is also completely independent of the furuncle. Thus, the outcome of K.O.'s case would be the same regardless of whether Dr. Lancaster had mentioned the furuncle. Overall, K.O.'s case is not persuasive.

V. Conclusion

K.O. claimed that the PCV vaccine caused A.F. to develop OMS. The evidence was not sufficient to establish the causal relationship between the vaccination and OMS. Consequently, K.O. is not entitled to compensation on behalf of her minor son, A.F.

The Clerk's Office is instructed to enter judgment in accord with this decision.

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master